"Special Scrutiny": A Targeted Form of Research Protocol Review

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Research participants require ongoing protection of the kind already established in law and regulation. However, "special scrutiny" for certain types of research is also needed. Three criteria for special scrutiny are 1) research that involves initial experiences of translating new scientific advances into humans, especially when the intervention is novel, irreversible, or both; 2) research with a known or credible risk for significant harm (death or serious disability are the clearest examples) to research participants as a consequence of the experimental intervention *and* with no potential for offsetting direct medical benefit; or 3) research with a protocol that raises ethical questions about research design or implementation for which there is no consensus. Special scrutiny recognizes that not all research protocols are equally ethically challenging and aims to provide appropriate protection for all research participants.

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Human participant research is now conducted in a dramatically changed environment from that of the 1970s, when the current regulatory and institutional framework for protecting the rights and welfare of participants was largely formulated. Take, for example, increasing privatization and globalization of research; a growing number of complex multisite and office-based trials with treating physicians as researchers; and the rapid development in the pipelines for novel agents, many based on genomic and proteomic discoveries. Recently, concern about bioterrorism and the spread of new or resurgent infectious diseases has intensified pressure for rapid development and introduction of vaccines and treatments.

Consequently, institutional review boards are faced not only with traditional issues of informed consent, voluntariness, and participant selection but also with those raised by novel procedures; uncertain or unknown risks; and increasing pressures from external sources, such as sponsors, regulators, and the public. All this happens in an environment of scarce resources, not the least of which is time.

The traditional mechanisms to protect participants—informed consent, voluntariness, and special regulations for "vulnerable" groups, such as prisoners and children (1, 2)—are arguably necessary but have never been sufficient. The 4 research participants whose deaths recently stimulated concern about the adequacy of the current system to provide appropriate protections in research did not belong to groups considered to be vulnerable under current regulations, and it seems that all of them were capable of providing informed and voluntary consent (3, 4). However, aspects of each protocol and its implementation and oversight were flawed (5–10).

Given such shortfalls, we propose a focused, "special" kind of scrutiny for research that raises serious moral challenges. Of course, special scrutiny has precedents. The Recombinant DNA Advisory Committee (RAC) was created in 1974 to set safety standards for recombinant DNA research. In 1984, the RAC established a working group to consider human research protocols, but the charge of this working group was limited in 1996. In 1977, the federal government created an Ethics Advisory Board to review fetal research and in vitro fertilization studies, but in 1980, its charter was not renewed. In 1996, federal regulations on consent waivers for emergency research were enacted, requiring institutional review boards to implement special types of review involving community consultation and public notification (11). Some institutional review boards may already conduct a level of special scrutiny, such as for phase I oncology trials. In addition, professional groups have considered the risks of certain procedures, such as maternal fetal surgery for spina bifida (12). These efforts were created under different auspices, involved different mechanisms, and were limited responses to specific problems.

We offer 3 criteria that individually or combined should trigger special scrutiny, and we discuss some ways to possibly implement special scrutiny in the current system of oversight. Under the current regulatory approach, research protocols can be exempt, eligible for expedited review, or subject to full review by an institutional review board. If exempt or expedited reviews are the least intensive points on this spectrum, special scrutiny is its opposite, the most intensive end. *Intensive* does not necessarily mean time-consuming, however. Where speed is essential, special scrutiny can take place through a highly focused review. Special scrutiny should allow institutional review boards to better manage their limited time and resources by freeing them from spending unnecessary effort on more routine research protocols.

When Does a Research Protocol Warrant Special Scrutiny?

Special scrutiny is appropriate when research projects are, in some morally relevant sense, "outliers," presenting novel or ethically challenging questions, situations, and strategies or a challenge to the status quo. Institutional review boards, investigators, and sponsors are challenged to recognize and respond to the moral complexities of a protocol before it is implemented, not only after it may be criticized in the scientific or lay press. We propose 3 crite-

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Table. **Criteria for and Examples of Research Warranting Special Scrutiny**

Criterion	Examples
Initial translation of scientific advances into humans	New implantable devices (for example, artificial hearts) Xenotransplantation New compounds
Risk for significant harm *and* no potential for offsetting direct medical benefit	Bronchoprovocation Washout trials with psychiatric patients Sham surgery (for example, involving craniotomy)
Ethical questions about research for which there is no authoritative consensus	Placebo trials where an effective treatment exists Imaging trials involving severely cognitively impaired persons who do not give assent Smallpox vaccine trials in children

ria for special scrutiny. These criteria are intended to alert institutional review boards to the potential need for special scrutiny. The examples we offer come from recent experience but do not exhaust future possibilities (**Table**).

Criterion 1. The research involves initial experiences of translating new scientific advances to studies in humans, especially when the intervention is novel, irreversible, or both. Such research includes investigational drugs, biologics, devices, or procedures that may pose unknown risk to participants. Consider, for example, "proof of concept" research—that is, research that involves initial attempts to determine whether a laboratory discovery or hypothesis with potential clinical applicability works as expected when tried in humans. The risks associated with such new drug compounds or new devices (such as artificial hearts) cannot be fully characterized until they are tried in humans and may be irreversible, thereby necessitating special scrutiny (13–15). Similarly, the uncertain risks associated with transplanting animal parts into humans in xenotransplantation may have implications for the recipients and others that call for careful prospective review (16–18).

Criterion 2. Without potential for offsetting direct medical benefit, there is a known or credible risk for significant harm (death or serious disability are the clearest examples) to humans as a consequence of the experimental intervention. Bronchoprovocation, for example, may be used in physiology studies with volunteers who do not have lung disease (19). Because these participants cannot benefit from the procedure, special scrutiny is required to set acceptable limits and safety procedures. Furthermore, this criterion applies to some research with patients. For example, psychiatric patients who discontinue their regular medications before receiving investigational drugs are exposed to known risks with no benefits during the "washout" period (20–22). In addition, patients with Parkinson disease undergoing sham surgery in the control group of studies involving the implantation of fetal cells through bur holes in their skull are exposed to risk without any possibility of expected benefit (23–26).

Criterion 3. The protocol raises ethical questions about research design or implementation for which there is no consensus or there are conflicting or ambiguous guidelines. For example, the use of placebos in international clinical research, especially trials in which antiretroviral agents have been given to some, but not all, pregnant women with HIV infection, has caused considerable controversy and discussion about which there is no consensus (27–30). Thus, special scrutiny would be indicated for research using placebos when there is a known, effective treatment for a condition, such as hypertension (31). In addition, imaging trials involving severely cognitively impaired persons who do not give assent, while not physically harming the participants, expose them to high levels of distress (32, 33). Smallpox trials in children, proposed because of fear of bioterrorism, raise questions not only of acceptable research in children but also of the level of actual risk for infection compared with the risks of vaccination (34–36).

Who Should Determine When Special Scrutiny Is Warranted?

Without regulatory guidance, institutional review boards may have to establish their own thresholds and conditions for special scrutiny. However, policymakers responsible for establishing procedures and delineating responsibilities for research oversight should specify conditions and procedures for special scrutiny. Of course, sponsors are uniquely positioned to identify a need for special scrutiny. Similarly, investigators developing research protocols should examine aspects of their research that might trigger the need for special scrutiny, including the environment in which they work; the context of their research; or their own, collaborators', or sponsors' financial or nonfinancial conflicts of interest (37).

An open question is whether, either before or after review by an institutional review board or in lieu of one, at least some research that requires special scrutiny should be reviewed by a standing regional or national committee with particular expertise. The RAC is a possible model (38).

What Should the Process of Special Scrutiny Include?

Special scrutiny is a more intense process of review than that ordinarily applied to most research. For example, when using special scrutiny, reviewers should not rely on the investigator's characterization of the risks but should

conduct their own independent review to ensure that all relevant data about risks and potential benefits are up-to-date, comprehensive, and carefully analyzed. Similarly, consultation with relevant experts or community groups should be routine, rather than the exception. Although some institutional review boards already carry out such procedures, special scrutiny provides a more systematic way of engaging them.

What Special Protections or Procedures Might Be Recommended or Implemented Because of Special Scrutiny?

Special scrutiny involves the same basic options available as standard review: approval, disapproval, or modification. Special scrutiny may, however, lead more frequently to recommending modification to incorporate additional protections. For example, reviewers might require more frequent or sequential reviews. They might approve a research project for a few participants but require a review of that experience before allowing enrollment of additional participants. Another possibility is for reviewers to recommend additional monitoring of the participants or data, for example, by creating a data safety and monitoring board for even a small trial or by integrating an independent monitor into study operations. For some complicated and high-risk research, reviewers may recommend independent monitoring of the consent process or rigorous evaluation of the participants' understanding of the research protocol. For other research, reviewers could recommend more stringent stopping rules than might ordinarily be used. Although many of these strategies can be and already are used by institutional review boards, the institutional review board or other review body would have a lower threshold for using them for research that deserves special scrutiny.

Future Challenges

The concept of special scrutiny recognizes that not all research protocols are equally ethically challenging and aims to enhance protection of the rights and welfare of all research participants. At the opposite end of the spectrum from expedited review, special scrutiny may include different levels of review and may result in requiring certain additional protections. Developing appropriate ways for investigators, sponsors, policymakers, and institutional review boards to identify when and how to implement special scrutiny should be a broad, collaborative process.

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